Novel antipsychotics for patients with bipolar disorder: a systematic review

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Authors' objectives
To assess the efficacy of novel antipsychotic drugs (olanzapine, risperidone, quetiapine and clozapine), both as monotherapy and as add-on therapy, for acute and maintenance treatment of bipolar disorder.

Searching
EMBASE, MEDLINE, TOXLINE and PsycINFO were searched from 1985 to 2000 for publications in any language. In addition, database alerts/updates were established on Adis LMS Drug Alerts, Adis Newsletters, Current Contents Search, EMBASE Alert, MEDLINE, Pharmaceutical News Index, PsycINFO and TOXLINE. The Cochrane Library was also searched and updated to Issue 2, 2001. The search terms were reported in the paper.

Websites of health technology assessment and near technology assessment agencies, specialised databases such as the NHS Centre for Reviews and Dissemination (University of York), and other information sources on the Internet (via Google) were also searched. The searches were supplemented by handsearches of selected journals and documents in the CCOHTA (Canadian Coordinating Office for Health Technology Assessment) library collection and the bibliographies of selected papers. Manufactures of the different novel antipsychotics were contacted for information on unpublished studies. All published (including abstracts) and unpublished studies were included.

Study selection

Study designs of evaluations included in the review
Prospective randomised controlled trials (RCTs), both parallel and crossover design, were included.

Specific interventions included in the review
Trials were included if they compared any of the novel antipsychotic drugs with placebo, classical antipsychotics, or other mood-stabilising agents such as lithium, valproate and carbamazepine. Trials comparing one novel antipsychotic with another novel antipsychotic, and trials that considered a novel antipsychotic in combination with other drugs, were also included.

Participants included in the review
Males and females of all ages with a diagnosis of bipolar disorder by any criteria, with all sub-types of bipolar mood disorder (rapid cycling, type I and type II) were included.

Outcomes assessed in the review
The outcomes of interest for the acute treatment phase were: clinical efficacy, defined as an improvement in both manic and depressive episodes; total drop-outs from trial; the number of patients withdrawing from the trial due to non-compliance; the number of patients withdrawing from the trial due to side-effects; and any adverse effect(s), such as extrapyramidal side-effects, during the trial.

The outcomes of interest for the maintenance treatment phase were: relapse (however defined, including re-admission to hospital); time to relapse; symptoms of mania or depression during follow-up, however measured; total drop-outs from the trial; and any adverse effect(s) experienced during the trial.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed potentially relevant studies for inclusion. Any disagreements were resolved by discussion and a third reviewer was available to adjudicate any persisting differences.

Assessment of study quality
The quality of the studies was assessed using the Jadad scale, which includes appropriateness of randomisation and
double-blinding, and a description of withdrawal and drop-outs. Information about allocation concealment to the
intervention group was also recorded. Two reviewers assessed the quality of the studies independently.

Data extraction
Two reviewers independently extracted data on the participant characteristics, intervention details and outcome
measures, from the included studies.

Methods of synthesis
How were the studies combined?
For binary efficacy outcomes, a pooled odds ratio (OR) with 95% confidence intervals (CIs) was calculated using a
fixed-effect model. For continuously distributed outcomes, the weighted mean differences (WMDs) were calculated.
Intention-to-treat data were used when available. Where this was not possible, end point data for persons completing the
trials were used. Qualitative data were presented descriptively.

How were differences between studies investigated?
Tests of heterogeneity were conducted. In trials that involved heterogeneous groups of participants, in particular
schizoaffective disorder and recurrent unipolar depression, the data were separated into diagnostic groups where
possible.

Results of the review
Eight RCTs with a total of 705 participants met the inclusion criteria.

The quality assessment (Jadad scale) showed that four studies were of moderate quality (scoring 3 to 4) and four were
of low quality (scoring 0 to 2). Allocation concealment was not described clearly in any of the studies.

The included studies assessed olanzapine, risperidone and clozapine. No studies considering the use of quetiapine were
identified. No studies comparing one novel antipsychotic to another were identified. Information on patient withdrawal
due to non-compliance was not described clearly in any of the studies.

Novel antipsychotic drugs as monotherapy in acute treatment of mania (4 RCTs). The pooled analysis of data from the
two RCTs comparing olanzapine with placebo showed that olanzapine was more effective than placebo when various
outcome measures were considered. Significant differences in favour of olanzapine over placebo were observed in the
following: Young Mania Rating Scale (YMRS) scores (WMD -5.94, 95% CI: -9.06, -2.81); Positive and Negative
Symptoms Scale scores (WMD -9.94, 95% CI: -14.72, -5.17); Clinical Global Impression scale scores (WMD -0.58,
95% CI: -0.93, -0.24); non-responders (i.e. patients achieving less than 50% decrease in total score on the YMRS) (OR
0.37, 95% CI: 0.22, 0.61); and number of drop-outs (OR 0.37, 95% CI: 0.22, 0.60). Olanzapine caused a significant
weight gain compared with placebo (WMD 1.91 kg, 95% CI: 1.29, 2.53). No significant difference was observed
between olanzapine and placebo groups in relation to quality of life or extrapyramidal side-effects. Data relating to the
efficacy of olanzapine versus other agents, and any of the other novel antipsychotics as monotherapy for the acute
treatment of mania was limited and was not transparent.

Data relating to the efficacy of novel antipsychotics as add-on therapy for the acute treatment of mania was limited (3
trials) and was not transparent. The studies showed no significant difference between novel antipsychotics and
traditional agents in the incidence of extrapyramidal side-effects, and the results of long-term therapy were not
available.

Authors’ conclusions
Currently, there is too little information to draw any meaningful conclusions concerning the use of antipsychotics in the
treatment of bipolar disorder. Given the high cost of these agents, and the lack of conclusive evidence concerning their
benefit over traditional therapies, a cautious approach is warranted when considering their use. This is a rapidly
changing field and other trials with new information will soon be completed.
**CRD commentary**
The authors clearly set out their objective and this was supported by a priori inclusion criteria relating to the participants, outcomes, intervention and study design. The literature search was extensive with no language restrictions, and attempts were made to retrieve unpublished data. The validity of the included studies was assessed systematically, and the study details were presented clearly in tabular format. The pooling was appropriate, and details relating to how the review process was carried out were provided. The authors’ conclusions follow from the results presented.

**Implications of the review for practice and research**
The authors did not state any implications for further research and practice.

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